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Novel chiral 1,3,2-dioxaphosphorinanes

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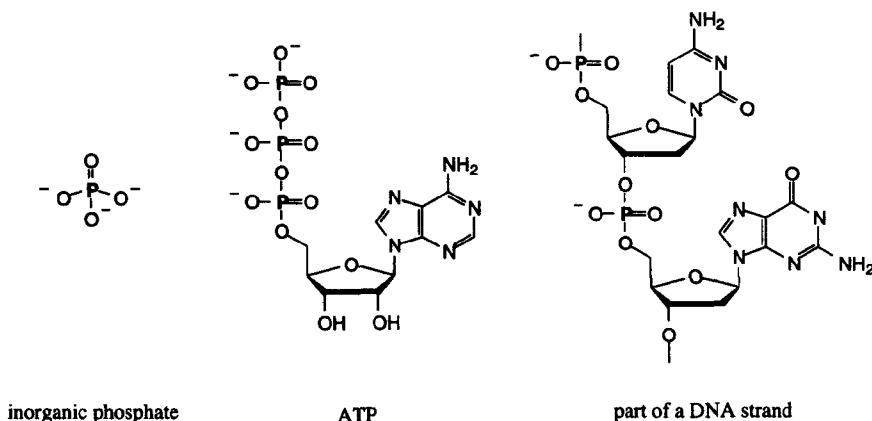
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Introduction

1.1 Phosphorus¹

Phosphorus is everywhere. It is present in a multitude of forms in nature and is essential to life. Phosphorus containing materials range from calcium phosphate in bone and teeth *via* the biochemical energy transfer agent adenosine triphosphate (ATP) to the essence of life itself in the form of the carriers of genetic information, the nucleic acids RNA and DNA. In nature phosphorus is found almost exclusively in the pentavalent oxidation state.



Scheme 1.1. Phosphorus in nature

The German Hennig Brand discovered phosphorus in 1669. Upon distillation of urine he obtained a material that glowed in the dark and ignited in air. It was called phosphorus (Greek for *light bearing*) because of these properties. Phosphorescence, however, is not a characteristic of phosphorus compounds, quite the contrary, most phosphorescent materials do not contain the element.

¹ (a) For a detailed discussion on all aspects of phosphorus see: Corbridge, D.E.C. *Phosphorus. An Outline of its Chemistry, Biochemistry and Technology*. Elsevier Science Publishers, Amsterdam, The Netherlands, 1990. (b) See also: Hartley, F.R. in *The Chemistry of Organophosphorus Compounds*, Vol. 1, Hartley, F.R., Ed. Wiley: Chichester, England, 1990, p. 1.

1.2 Phosphorus: the element

Phosphorus, symbol P, atomic number 15, atomic weight 30.9738, exists as a single stable isotope ^{31}P with a nuclear spin of $\frac{1}{2}$.¹ Its relatively high sensitivity (0.066 vs. $1.76 \cdot 10^{-4}$ for ^{13}C , corrected for natural abundance) for nuclear magnetic resonance makes it possible to study reaction kinetics and analyse complex reaction mixtures due to the simplicity of proton-decoupled phosphorus ($^{31}\text{P}\{^1\text{H}\}$) NMR spectra compared with ^1H NMR spectra. The spectral width of phosphorus NMR is large: from -488 ppm for P_4 to +277 ppm for PBr_3 , every class of phosphorus compound having its own region in the spectrum.

1.3 Structure and bonding^{1b}

Simple approaches like valence shell electron pair repulsion (VSEPR) do not satisfactorily describe structure and bonding in tervalent organic phosphorus compounds. Walsh diagrams form a more accurate, albeit qualitative, representation of the bonding in phosphines. For quantitative predictions one has to rely upon abstract and time-consuming quantum chemical calculations.

The involvement of d-orbitals in bonding to phosphorus still is a disputed issue. Back-donation of transition metal electrons into vacant d-orbitals has often been proposed as the reason for the stability transition metal complexes of tervalent phosphorus. However, it is now accepted that back-bonding plays a role only in complexes of PF_3 and phosphites and that not d-orbitals on phosphorus but σ^* -orbitals are the acceptor orbitals.

Another class of compounds where d-orbitals were thought to be involved in bonding, is the pentavalent phosphorus chalcogenides $\text{R}_3\text{P}=\text{E}$ ($\text{E} = \text{O}, \text{S}, \text{Se}, \text{Te}$).² The generally applied representation of 'pentavalent' phosphoryl compounds as $\text{R}_3\text{P}=\text{O}$ violates the Langmuir octet rule. The representation is also misleading because it implies a double bond between phosphorus and oxygen which suggests the possibility of addition reactions.

Numerous alternative models for the phosphoryl PO bond have been put forward.² Back-donation of oxygen lone pair electrons into anti-bonding orbitals of e symmetry on phosphorus produces two mutually perpendicular half π -bonds (Figure 1.1, left).³

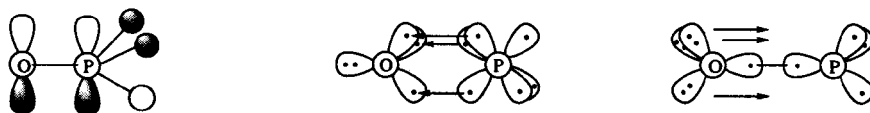


Figure 1.1. Models for the phosphoryl PO bond. Left: π -backbond; middle: Ω -model; right: triple back bond

² Gilheany, D.G. in *The Chemistry of Organophosphorus Compounds*, Vol. 2, Hartley, F.R., Ed. Wiley: Chichester, England, 1992, p. 1.

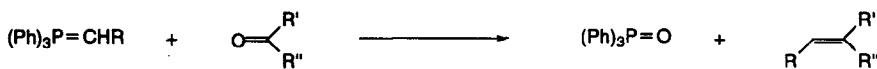
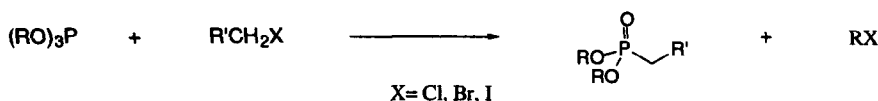
³ Knutzelnigg, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 272.

Ab initio calculations by different procedures resulted in the Ω - and triple back bond models.⁴ Although the $R_3P=O$ representation is clearly an oversimplification, it is still widely adapted since it reflects the bond strength and interatomic distance in phosphoryl compounds.

The nature of the PO bond itself being uncertain, the correct formulation of the coordinative bond to a metal atom seems out of reach. From X-ray diffraction studies it is clear that M–O bonds have multiple bond character with M–O–P angles varying from 113 to 180°. In contrast, M–E bonds (E = S, Se, Te) are single bonds with M–E–P angles varying from 96 to 120°.⁵

1.4 The organic chemistry of phosphorus

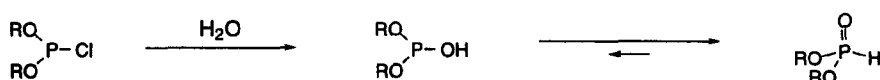
Synthetic organophosphorus compounds were first reported in the 19th century; alkyl phosphates in 1820 and phosphines in 1840. The organic chemistry of phosphorus is dominated by two oxidation states: P^{III} and P^V . Phosphorus forms strong bonds with oxygen, and formation of this bond is the driving force in many reactions typical of phosphorus, amongst others the Arbuzov reaction and the Wittig reaction.



Scheme 1.2. The Arbuzov (top) and Wittig reactions

Most trivalent organophosphorus species are sensitive to oxidation by atmospheric dioxygen or hydrolysis, forming pentavalent phosphoryl compounds.

A special case is formed by the simple dialkyl phosphites: they exist in equilibrium with tautomeric H-phosphonates and are not readily oxidized.



Scheme 1.3. Tautomerism in dialkyl phosphites/dialkyl H-phosphonates

The spectroscopic data for, and reactivity of these compounds reflect the position of the phosphite/phosphonate equilibrium. Resonances in ^{31}P NMR for these compounds are found

⁴ (a) Schmidt, M.W.; Yabushita, S.; Gordon, M.S. *J. Chem. Phys.* **1984**, *88*, 382. (b) Messmer, R.P. *J. Am. Chem. Soc.* **1991**, *113*, 433.

⁵ Lobana, T.S. in *The Chemistry of Organophosphorus Compounds*, Vol. 2, Hartley, F.R., Ed. Wiley: Chichester, England, 1990, p. 409.

around 0 ppm, characteristic for pentavalent species. The H-phosphonate hydrogen atom displays a very large coupling constant ($J_{PH} \approx 600\text{--}700\text{ Hz}$), indicative of its being directly bonded to phosphorus. Dialkyl phosphites are not readily oxidized.

Contrastingly, alkali metal derivatives of H-phosphonates have dialkyl phosphite character: infrared spectra lack the $\nu(\text{P}=\text{O})$ vibrational band and feature a $\text{P}-\text{O}^-$ band instead. The ^{31}P NMR resonance is found in the phosphite range.⁶ The anions generally react as *P*- rather than *O*-nucleophiles.

1.5 Phosphorus-based ligands

1.5.1 Tervalent phosphorus in ligands^{1,7}

Tervalent phosphorus has a free electron pair that can be donated to empty metal orbitals to form coordination complexes. Coordination compounds of PF_3 , phosphines (e.g. PPh_3) and phosphites (e.g. $\text{P}(\text{OEt})_3$) have all been described, as well as many intermediate forms like phosphinites (e.g. Ph_2POEt) and phosphonites (e.g. $\text{PhP}(\text{OEt})_2$).

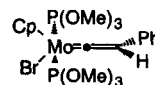
Bonding capacity of tervalent phosphorus ligands to metals is often described in terms of σ -donor ability and π -acceptor ability.⁷ The ratio between π -acceptor ability/ σ -donor ability can be related to carbonyl stretching frequencies in metal carbonyl complexes.⁸ Generally speaking, phosphines are stronger σ -bases whilst phosphites are stronger π -acids. Therefore, phosphines will readily complex electron poor metals in high oxidation states, whereas phosphites prefer electron rich metals in their lower oxidation states. Apart from electronic factors, size of substituents on phosphorus plays a major role in determining the relative stability of the metal phosphorus bond.⁹



ref. 10



ref. 11



ref. 12

Scheme 1.4. Examples of complexes of tervalent phosphorus ligands

Complexes of tervalent phosphorus ligands are known for metals throughout the transition series; examples of PF_3 ,¹⁰ PPh_3 ¹¹, and $\text{P}(\text{OMe})_3$ ¹² complexes are depicted in Scheme 1.4.

⁶ Nagar, P.N. *Phosphorus, Sulfur and Silicon* **1993**, 79, 207.

⁷ McAuliffe, C.A.; Levason, W. *Phosphine, Arsine and Stibine Complexes of the Transition Metals*, Elsevier Scientific Publishing Company: Amsterdam, The Netherlands, 1979.

⁸ Cotton, F.A.; Kraihanzel, C.S. *J. Am. Chem. Soc.* **1962**, 84, 4432.

⁹ Tolman, C.A. *Chem. Rev.* **1977**, 77, 313.

¹⁰ Sikora, D.J.; Rausch, M.D.; Rogers, R.D.; Atwood, J.L. *J. Am. Chem. Soc.* **1981**, 103, 982.

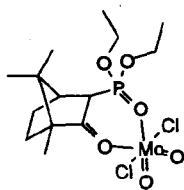
¹¹ Chen, Y.-J.; Wang, J.-C.; Wang, Y. *Acta Cryst.* **1991**, C47, 2441.

¹² Beevor, R.G.; Green, M.; Orpen, A.G.; Williams, I.D. *J. Chem. Soc., Dalton Trans.* **1987**, 1319.

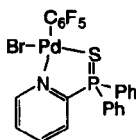
Many complexes have been collected and classified according to the different groups in the Periodic Table.¹³

1.5.2 Pentavalent phosphorus in ligands^{1,5,8}

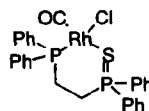
Phosphoryl oxygen, sulfur, selenium, and tellurium can donate electron density to metal atoms, forming coordination compounds. Compounds like trioctylphosphine oxide are efficient extractants for lanthanides and actinides.¹⁴ Combination with other donor atoms to give bi- or polydentate ligands enhances the affinity for transition metals. Examples with oxygen,¹⁵ nitrogen¹⁶, and trivalent phosphorus¹⁷ have been described.



ref. 15



ref. 16



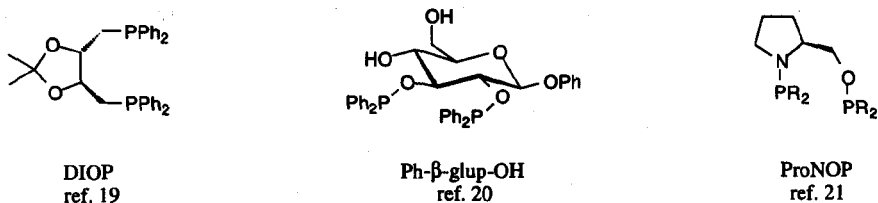
ref. 17

Scheme 1.5. Examples of complexes of pentavalent phosphorus ligands

1.6 Stereochemistry of organophosphorus compounds

With the ever growing importance of asymmetric catalysis,¹⁸ synthesis of chiral phosphorus ligands has received much attention in recent years. The 'chiral pool' is a rich source of starting materials for the syntheses of a variety of chiral phosphines, phosphinites, phosphonites, and other derivatives. Typical examples include DIOP¹⁹, derived from tartaric acid, Ph- β -glup-OH,²⁰ based on the sugar glucose and ProNOP,²¹ based on the amino acid proline.

- 13 (a) *Comprehensive Coordination Chemistry*, Wilkinson, G.; Gillard, R.D.; McCleverty, J.A., Eds., Pergamon Press: Oxford, 1987. (b) *Comprehensive Organometallic Chemistry*, Wilkinson, G.; Stone, F.G.A.; Abel, E.W. Eds., Pergamon Press: New York, 1982.
- 8 Ionic pentavalent phosphorus is left out of consideration.
- 14 Nicol, M.J.; Fleming, C.A.; Preston, J.S. in reference 13a, Chapter 63.
- 15 Gahagan, M.; Mackie, R.K.; Cole-Hamilton, D.J.; Cupertino, D.C.; Harman, M.; Hursthouse, M.B. *J. Chem. Soc., Dalton Trans.* **1990**, 2195.
- 16 Casares, J.A.; Coco, S.; Espinet, P.; Lin, Y.-S. *Organometallics* **1995**, *14*, 3058.
- 17 Baker, M.J.; Giles, M.F.; Orpen, A.G.; Taylor, M.J.; Watt, R.J. *J. Chem. Soc., Chem. Commun.* **1995**, 197.
- 18 Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, 1994.
- 19 Kagan, H.B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
- 20 Kumar, A.; Oehme, G.; Roque, J.P.; Schwarze, M.; Selke, R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2197.
- 21 Agbossou, F.; Carpentier, J.-F.; Hatat, C.; Kokel, N.; Mortreux, A.; Betz, P.; Goddard, R.; Krüger, C. *Organometallics* **1995**, *14*, 2480.



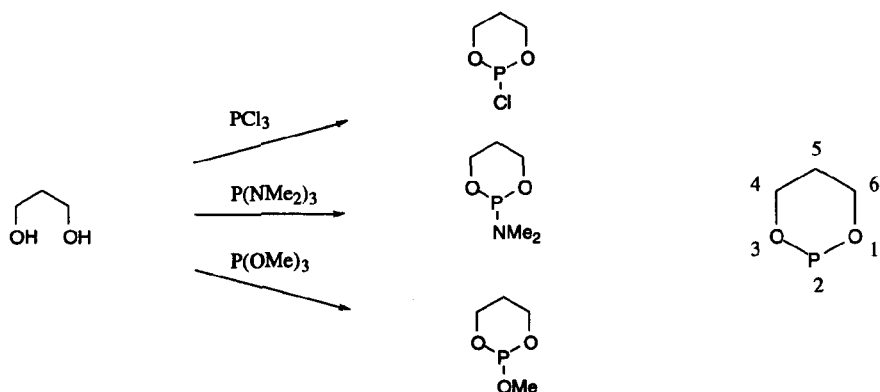
Scheme 1.6. Tervalent phosphorus ligands derived from naturally occurring chiral building blocks

The vast majority of tervalent and pentavalent phosphorus compounds are tetrahedral. Hence, phosphorus can be, and often is, a stereogenic centre. In contrast with chiral nitrogen, chiral tervalent phosphorus is configurationally stable.

Compounds with a stereogenic phosphorus atom are referred to as being P-chiral. A recent review describes the synthesis of a host of P-chiral ligands.²²

1.7 Dioxaphosphorinanes

This thesis deals with the synthesis of 1,3,2-dioxaphosphorinanes. Dioxaphosphorinanes are six-membered rings containing, apart from carbon, one phosphorus atom and two oxygen atoms. 1,3,2-Dioxaphosphorinanes are generally synthesized from a 1,3-diol and a simple phosphorus compound, *e.g.* PCl_3 , $\text{P}(\text{NMe}_2)_3$, $\text{P}(\text{OMe})_3$.



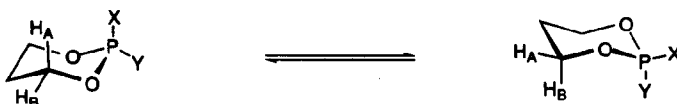
Scheme 1.7. General synthesis and numbering scheme of 1,3,2-dioxaphosphorinanes

²² Pietrusiewicz, K.M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375.

1.7.1 Conformational analysis of 1,3,2-dioxaphosphorinanes

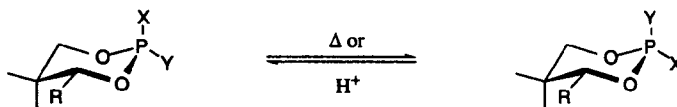
The conformations of 1,3,2-dioxaphosphorinanes and 1,3,2-oxazaphosphorinanes have been widely studied over the last decades.²³ X-Ray crystallography,²⁴ ³¹P NMR²⁵ and multidimensional ¹H NMR studies, and quantum chemical calculations are important tools for conformational analysis. With the ever increasing power of computer systems and refinement of basis sets used, the importance of computational chemistry is growing.

Many 1,3,2-dioxaphosphorinanes adopt a chair conformation, slightly flattened at the phosphorus end, due to relatively long P–O bonds. Unsubstituted and symmetrically 5,5-disubstituted 1,3,2-dioxaphosphorinanes are highly mobile and undergo rapid chair-chair interconversion.



Scheme 1.8. Chair-chair interconversion in unsubstituted 1,3,2-dioxaphosphorinanes

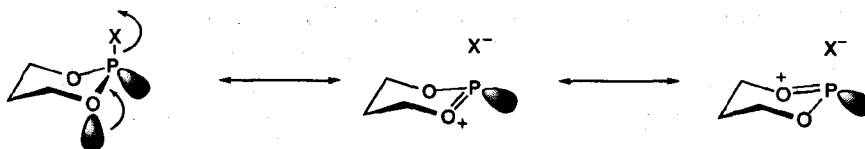
With the introduction of larger substituents at the 4- or 5-positions, the ring becomes rigid and one of the chair conformations becomes predominantly populated. These systems are referred to as *anameric*.²⁶ The two diastereomers will have reasonable configurational stabilities, but will equilibrate in solution, a process that is accelerated by heating or addition of traces of acid.



Scheme 1.9. Equilibration of anameric 1,3,2-dioxaphosphorinanes

With regard to the dioxaphosphorinanes described in this thesis, it is noteworthy that in tervalent systems, chloride and alkoxy groups prefer the axial position at phosphorus. This preference is generally ascribed to the anomeric effect,²⁷ *i.e.* stabilizing $n\text{-}\sigma^*$ interactions between lone pair electrons on the ring oxygen and the axial $\sigma^*\text{P-X}$ orbital,^{25b} in combination with reduced 1,3-*syn*-axial repulsions due to the relatively long P–O bonds.

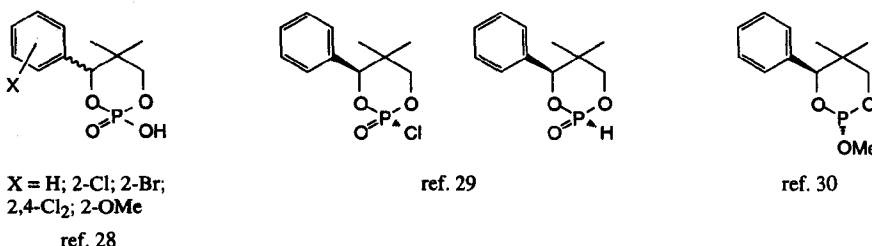
- ²³ Maryanoff, B.E.; Hutchins, R.O.; Maryanoff, C.A. in *Topics in Stereochemistry*, Allinger, N.L.; Eliel, E., Eds.; Wiley: New York, 1979, Vol. 11, p. 187.
- ²⁴ Corbridge D.E.C. *The Structure Chemistry of Phosphorus*, Elsevier: Amsterdam, 1974.
- ²⁵ (a) Bentrude, W.G.; Setzer, W.N. in *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*, Verkade, J.G.; Quin, L.D., Eds.; VCH: Deerfield Beach, 1987, p. 365. (b) Bentrude, W.G. in *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*, Quin, L.D.; Verkade, J.G., Eds.; VCH: New York, 1994, p. 41.
- ²⁶ Anteunis, M.; Tavernier, D.; Borremans, F. *Bull. Chim. Soc. Belges* **1966**, 75, 396.
- ²⁷ Bailey, W.F.; Eliel, E.L. *J. Am. Chem. Soc.* **1974**, 96, 1798.



Scheme 1.10. Representation of the anomeric effect

1.7.2 1,3,2-Dioxaphosphorinanes from this laboratory

In the Organic Chemistry Department of this University, chiral cyclic phosphoric acids have been developed for the classical resolution of chiral amines and amino acids.²⁸ Two P-chiral derivatives of these 1,3,2-dioxaphosphorinanes have been applied as derivatizing agents for the determination of enantiomeric excesses (e.e.) of amines, amino acids, and alcohols using ³¹P NMR spectroscopy.²⁹



Scheme 1.11. Chiral 1,3,2-dioxaphosphorinanes studied in this laboratory

Acylphosphonates and isocyanomethylphosphonates were prepared from the methylphosphite as chiral auxiliaries for diastereoselective condensation reactions.³⁰

1.8 Outline of this thesis

Chapter 2 deals with the synthesis and characterization of novel chiral pyridinyl-2-phosphonates based on the 1,3,2-dioxaphosphorinane fragment. The molecules described exhibit remarkable conformations that have been studied using (multidimensional) NMR spectroscopy and X-ray diffraction.

Chapter 3 describes the synthesis of novel chiral diols from a 'universal' chiral starting material. This allows for the synthesis of diols with a variety of steric and electronic characteristics.

- 28 (a) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508. (b) Van der Haest, A.D. thesis, University of Groningen, 1992.
- 29 Hulst, R.; Zijlstra, R.W.J.; De Vries, N.K.; Feringa, B.L. *Tetrahedron: Asymmetry* **1994**, *5*, 1701.
- 30 (a) Ebens, R.H.E.; Hulst, A.R.J.L.; Feringa, B.L., unpublished results. (b) Weener, J.-W.; Van Leusen, A.M., unpublished results.

One of these diols is applied in *Chapter 4* as structural basis for a number of diphosphites. A diphosphite derived from catechol has been characterized by X-ray diffraction, and a molybdenum complex of this diphosphite has been synthesized. Treatment of oily diphosphites with borane-tetrahydrofuran afforded crystalline, air-stable adducts that were purified by column chromatography.

A case of chiral self-recognition, accidentally found during diphosphite synthesis, is examined in *Chapter 5*. The degree of recognition and its origin were established.

In *Chapter 6*, the conformations of several pyridinyl-2-phosphonates, the synthesis of which is discussed in Chapter 2, are studied using molecular modelling techniques. The calculated optimized geometries correlate favorably with experimental data.